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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
CHEN, LIPING

ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 10/09/2002

8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/856,104	Applicant(s) BARSKY ET AL.	
	Examiner Liping Chen	Art Unit 1632	

-- The MAILING DATE of this communication appears on th cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 September 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *13-27* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-12,28 and 29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Status of the claims

A restriction was made on 08/05/2002. Applicant's election with traverse of Group I, claims 1-12, 28 and 29, in Paper No. 7, is acknowledged. The traversal is on the ground(s) that "a search into prior art with regard to the invention of the different Groups is so related that separate significant search efforts should not be necessary. Accordingly, there is no serious burden on the Examiner to collectively examine the different claim Groups of the subject application". This is not found persuasive because the method of Group I (claim 28 and 29) is directed to identifying a molecule whose expression level is modulated in inflammatory breast cancer using claimed Xenograft. The method used in Group I is at nucleic acid and protein level. It does not require techniques at cellular or organ level. However, technique(s) for detecting cellular or organ level changes are required in Group II-IV. Group II (claims 13-18), is directed to a method for evaluating at least one agent for treating inflammatory breast cancer, Group III (claims 19-22), to a method for evaluating at least one agent for identifying inflammatory breast cancer, and Group IV (claims 23-27), to a method for evaluating the potential of an agent for the prevention of lymphovascular invasion of carcinoma cells; each method differs from other by detecting a different agent with different function, which requires different technique(s) to accomplish, and each group has different target population. So a

different search will be required for each group as different technique(s) and targeting populations are present. Thus, the requirement is still deemed proper and is therefore made FINAL. Therefore, only Group I is examined in this office action.

Claims 13-27 are withdrawn as being to a non-elected invention.

Claims 1-29 are pending and claims 1-12, 28 and 29 are examined in this office action on the merits.

Priority

This is a 371 of PCT/US00/25299 filed 09/15/2000.

Priority claimed to provisional application 60/154,408 filed 09/17/1999.

Objection

The disclosure is objected to because of the following informalities:

This application does not contain an abstract of the disclosure as required by 37 CFR 1.72(b). An abstract on a separate sheet is required.

Page 12, line 15-16, states "ATCC as deposit no._____on _____". It is suggested this be filled in the ATCC deposit no. and the date of deposit, respectively.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4, 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a human inflammatory breast cancer xenograft growing within lymphatic and blood vessel channels of immunocompromised host, does not reasonably provide enablement for a human inflammatory breast cancer xenograft growing within lymphatic and blood vessel channels of immunocompetent host. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 1 is directed to a human inflammatory breast cancer xenograft, wherein the xenograft grows within lymphatic and blood vessel channels and comprises the following properties: i) does not express estrogen receptor and progesterone receptor; and ii) expresses P53, EGFR, MUC1 and E-cadherin; claim 2 is directed to the xenograft of claim 1 wherein the level of E-cadherin expressed by xenograft of claim 1 is at least two-fold greater than the level of E-cadherin expressed by a noninflammatory breast cancer xenograft; claim 3 is directed to the xenograft of claim 2 which expresses α-catenin and β-catenin and both of which are at least two-fold greater than the levels of α-catenin and β-catenin expressed by a

noninflammatory breast cancer xenograft; claim 4 is directed to the xenograft of claim 3 that does not express Her-2/neu; claim 28 is directed to a method of identifying a molecule whose expression is modulated in inflammatory breast cancer by comparing the expression in a xenograft which has properties of the xenograft of claim 1 and a cell having characteristics which are distinct from the human inflammatory breast cancer xenograft, and claim 29 is directed to the method of identifying a molecule of claim 28 is selected from the group consisting of: Northern Blotting, Southern blotting, Western blotting and polymerase chain reaction.

However, the specification only provide teaching of growing human inflammatory breast cancer xenograft (specification, page 16, line 20-21 and page 56, Example 1) within lymphovascular spaces (specification, page 60, line 7-8) in nude and scid mice. There is no evidence or teaching regarding how to grow human inflammatory breast cancer xenograft within lymphovascular spaces in immunocompetent mice or other immunocompetent host. With regard to Xenograft, Saadi et al. (Life Sci 62:365-387, 1998) teaches that Xenogeneic immune responses mediated by naturally-occurring antibodies and complement lead to hyperacute and acute vascular rejection of vascularized organ grafts and may also cause vascular rejection of cell and tissue grafts. Xenogeneic immune responses mediated by T lymphocytes and natural killer cells may cause acute cellular rejection (Saadi, Abstract). Gill (Ann N Y Acad Sci 944:35-46, 2001) teaches that most tissue

allografts or xenografts are spontaneously accepted in T cell-deficient mice (e.g. athymic nude or scid mice) despite the presence of functional innate immune system components such as natural killer (NK) cells, myeloid lineage cells, and complement pathways. Although these varied innate immune system elements greatly contribute to host reactivity, graft destructive response in mice appear to be fundamentally T cell-dependent (Gill, page 38, first full parag.). Gill further teaches to use immunoisolation strategies to prevent cell-cell contact between host and donor cells for preventing the rejection of cellular xenografts (Gill, Abstract) and points out the biomaterial used for immunoisolation must be compatible both with the grafted cells or tissues and with the host itself (Gill, page 36, last parag.). Gill further states that although preventing cell-cell contact is currently feasible and realistic, preventing exposure of the host to potentially small molecular weight donor-derived antigens may not be readily feasible (Gill, page 43, last parag.). Taken together the prior art teaches the fate of xenografts in an immunocompetent host is rejection, and nude and scid mice are exceptional as they are T cell-deficient and the xenograft response appear to be fundamentally T cell-dependent. Thus, the specification fails to teach the skilled artisan how to grow human inflammatory breast cancer xenograft within lymphovascular spaces in immunocompetent mice or other immunocompetent host to reach successful results without undue experimentation. Based upon the nature of the invention, the state of the prior art, lack of direction or guidance as how to grow human inflammatory breast cancer

xenograft within lymphovascular spaces in immunocompetent host without encountering rejection, the claimed invention would have required one skilled in the art to engage in an undue amount of experimentation without a predictable degree of success to achieve any specific and the breath of the invention.

Claims 1-4, 6-11, 28 and 29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for generating a human inflammatory breast cancer xenograft growing within lymphatic and blood vessel channels of immunocompromised host, or an in vitro culture of a human inflammatory breast cancer xenograft, or a non-human animal model comprising the xenograft claimed, wherein in each instance the xenograft comprises cells of MARY-X, does not reasonably provide enablement for a human inflammatory breast cancer xenograft having the properties of i) does not express estrogen receptor and progesterone receptor; and ii) expresses P53, EGFR, MUC1 and E-cadherin. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 1 is directed to a human inflammatory breast cancer xenograft, wherein the xenograft grows within lymphatic and blood vessel channels and comprises the following properties: i) does not express estrogen receptor and progesterone receptor; and ii) expresses P53, EGFR, MUC1 and E-cadherin; claim 2

is directed to the xenograft of claim 1 wherein the level of E-cadherin expressed by xenograft of claim 1 is at least two-fold greater than the level of E-cadherin expressed by a noninflammatory breast cancer xenograft; claim 3 is directed to the xenograft of claim 2 which expresses α-catenin and β-catenin and both of which are at least two-fold greater than the levels of α-catenin and β-catenin expressed by a noninflammatory breast cancer xenograft; claim 4 is directed to the xenograft of claim 3 that does not express Her-2/neu; claim 6 is directed to an in vitro culture of a human inflammatory breast cancer xenograft grows as spheroid and has the properties of xenograft of claim 1, claim 7 is directed to the in vitro culture of claim 6, where in the spheroid can attach to a cell monolayer, claim 8 is directed to the in vitro culture of claim 7, wherein the spheroid disadheres from the cell monolayer when exposed to a culture media containing absent Ca++ or anti-E-cadherin antibody, cliam 9 is directed to a method of generating the xenograft of claim 1 in an immunocompromised host, claim 10 is directed to non-human animal model for inflammatory breast comprising an xenograft having the properties of the xenograft of claim 1, claim 11 is directed to a animal model of cliam 10, wherein the immunocopromised host is a nude mouse, claim 28 is directed to a method of identifying a molecule whose expression is modulated in inflammatory breast cancer by comparing the expression in a xenograft which has properties of the xenograft of claim 1 and a cell having characteristics which are distinct from the human inflammatory breast cancer xenograft, and claim 29 is directed to the

method of identifying a molecule of claim 28 is selected from the group consisting of: Northern Blotting, Southern blotting, Western blotting and polymerase chain reaction.

Claims 1-4 are directed to a human inflammatory breast cancer xenograft has the properties of i) does not express estrogen receptor and progesterone receptor; and ii) expresses P53, EGFR, MUC1 and E-cadherin; claims 6-8 are directed to an in vitro culture that is based on the xenograft MARY-X (specification, page 29, line 8- 13, page 56, line 24 to page 57 line 11, and page 60, line 6 to page 65,line 7), which has the properties of the xenograft of claim 1; claims 10 and 11 are directed to non-human animal models that comprising a human inflammatory breast cancer xenograft having the properties of the xenograft of claim 1; and claims 28 and 29 are directed to methods that using xenografts having the properties of the xenograft of claim 1. According to the specification, the MARY-X xenograft is established directly from a 45-year-old female who presented with a warm and erythematous breast and ill-define mass (specification, page 56, line 6-7). Kleer et al. (Breast Cancer Res 2:423-429, 2000) teaches that inflammatory breast cancer (IBC) represents 1-6% of all breast cancers (Kleer, page 424, sec full parag.) and IBC tumors frequently lack expression of the cytosolic estrogen receptor (ER) (44% of IBC tumors are ER positive) and progesterone receptor (PgR) (30% of IBC tumors are PgR positive) (page 425, right col. third full parag.), and about 58% of IBC tumors are EGFR positive (Kleer, page 426, left col. line 10) and over 70% of cases

have a mutation in p53 (Kleer, page 426, left col. third full parag.). According to Kleer, the ER negative cases are about 56%, PgR negative cases are about 70%, EGFR positive cases 58% and P53 positive cases 30% in the population of IBC which is about 1-6% of all breast cancers. Thus, the chance of finding a patient who has IBC with all the claimed properties is very limited. Since the xenograft with the properties is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The specification does not provide any source for obtaining the inflammatory breast cancer having the properties of the xenograft of claim 1 for establishing the xenograft. Based upon the nature of the invention, the state of the prior art, lack of direction or guidance as how to obtain the human inflammatory breast cancer having all properties of the xenograft of claim 1, the claimed invention would have required one skilled in the art to engage in an undue amount of experimentation without a predictable degree of success to achieve any specific and the breath of the invention.

Claims 5 and 12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention consists of a human inflammatory breast cancer xenograft designated MARY-X, which has the properties of i) does not express estrogen receptor and progesterone receptor; and ii) expresses P53, EGFR, MUC1 and E-cadherin. According to the specification, the MARY-X xenograft is established directly from a 45-year-old female who presented with a warm and erythematous breast and ill-define mass (specification, page 56, line 6-7). Kleer et al. (Breast Cancer Res 2:423-429, 2000) teaches that inflammatory breast cancer (IBC) represents 1-6% of all breast cancers (Kleer, page 424, sec full parag.) and IBC tumors frequently lack expression of the cytosolic estrogen receptor (ER) (44% of IBC tumors are ER positive) and progesterone receptor (PgR) (30% of IBC tumors are PgR positive) (page 425, right col. third full parag.), and about 58% of IBC tumors are EGFR positive (Kleer, page 426, left col. line 10) and over 70% of cases have a mutation in p53 (Kleer, page 426, left col. third full parag.). According to Kleer, the ER negative cases are about 56%, PgR negative cases are about 70%, EGFR positive cases 58% and P53 positive cases 30% in the population of IBC which is about 1-6% of all breast cancers. Thus, the chance of finding a patient who has IBC with all the claimed properties is very limited. Further, MARY-X has the property of being Her-2/neu negative (specification, page 13. line 15-16). Kleer et al. (Mod Pathol 14:458-464, 2001) compares 20 IBC patient, and 56% of them are her2/neu positive (Kleer, 2001, page 461, Table 1). Kleer et al. states that no association was found between E-cadherin expression and ER, PR status, or

Her2/neu overexpression (Kleer, 2001, Abstract). Thus, the limitation for finding a patient who has IBC with all properties of MARY-X will be further limited. The xenograft of claim 5 and non-human model of claim 12 require a human inflammatory breast xenograft which has the properties of MARY-X. Since the xenograft with the properties is essential to the claimed invention, it must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. If the xenograft is not so obtainable or available, the requirements of 35 U.S.C. 112, regarding "how to make", may be satisfied by a deposit of the xenograft. If the deposits are made under the terms of the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the xenograft has been deposited under the Budapest Treaty and that the xenograft will be irrevocably and without restriction released to the public upon the issuance of a patent, would satisfy the deposit requirement.

It the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 CFR 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that

(a) during the pendency of this application, access to the invention will afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request of for the effective life of the patent, whichever is longer; and,

(d) a test of viability of the biological material at the time of deposit (see 37 CFR 1.807);

and,

(e) the deposit will be replaced if it should ever become inviable.

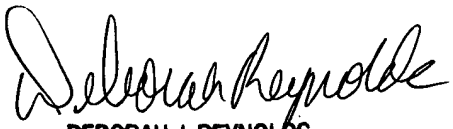
Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Liping Chen, whose telephone number is (703) 305-4842. The examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time). Should the examiner be unavailable, inquiries should be directed to Deborah Reynolds, Supervisory Primary Examiner of Art Unit 1632, at (703) 305-4051. Any administrative or procedural questions should be directed to Pauline Farrier, Patent Analyst, at (703) 305-3550. Papers

related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-8724.

Liping Chen, Ph.D.
Patent Examiner
Group 1632



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